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REMARKS

Amendment to the Claims

Claim 18 has been cancelled which renders the previous objection moot. Claims 1, 2, 4-8, 11-15 and 19-24 are still pending. It is believed that no new matter has been added.

35 U.S.C. 103(a) rejections

- (1) Claims 1, 2, 4-8, 11-15, 18 and 19 were rejected by the examiner as being obvious over Giacomoni (WO 96/26711)

Background

The claims as amended are directed toward a method of treating rosacea, however, the first ten lines of the examiner's rejection appear directed more towards a rejection of a composition claim. While it is understood that it is necessary to disclose that elements of the composition used in the applicants method claims are also taught by Giacomoni, the examiner concedes that "While the Giacomoni reference encompasses the claimed method of treating rosacea by applying to a patient a NO-synthase inhibitor-containing composition, it is deficient in the sense that it does not provide guidance as to selecting rosacea among various other skin conditions."

The applicants agree with the examiner's assessment of the method of treating rosacea claims up to this point but disagree with the rationale that the examiner uses to assert that the applicants' claimed invention is obvious over Giacomoni.

Context of Giacomoni's teaching is not directed toward treating rosacea

The evidence that Giacomoni teaches the treatment of rosacea, the examiner directs attention to a passage in Giacomoni which teaches that his compositions "are ideal for use" in the treatment of "dermatological complaints associated with a keratinisation disorder relating to differentiation and proliferation, particularly for treating...rosaceous acne."

To a layman, the examiner's comment would appear to suggest an almost explicit teaching from within Giacomoni as there is no further description about the passage from which the quoted text was obtained. However, this is not an accurate depiction of the context within which Giacomoni made his disclosures and one of ordinary skill in the art reading the same passage referred to by the examiner would not come to the conclusion that the applicants claimed invention is obvious over Giacomoni.

Determination of obviousness requires consideration "as a whole" of both the applicants' invention and the invention of the prior art and does not allow for improper picking and choosing elements to meet the requirements of the applicants claims. For the record, the passage from Giacomoni is reproduced below with the examiner's quotations being in bold and italics:

"The pharmaceutical compositions according to the invention ***are ideal for use*** in the following areas of treatment, these treatments being particularly well adapted when these compositions contain retinoids:

- 1) for treating ***dermatological complaints associated with a keratinisation disorder relating to differentiation and proliferation,***

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particularly for treating common blackheads, polymorphous and *rosaceous acne*, nodulocystic acnes, conglobata, senile acnes, secondary acnes such as solar acne, medicinal or professional acne;

- 2) for treating other types of keratinisation disorders, particularly ichthyoses, ichthyosiform conditions, Darrier's disease, palmoplantar disease, palmoplantar keratodermias, leucoplasias and leucoplasiform conditions, cutaneous lichen of the (oral) mucous membrane;
- 3) for treating other dermatological complaints associated with a keratinisation disorder with an inflammatory and/or immuno-allergic component, and in particular all forms of psoriasis, whether it be cutaneous, mucous or ungula, and even psoriatic rheumatism, or even cutaneous atopia, such as eczema or respiratory atopia, or even gingival hypertrophy; the compounds may also be used in certain inflammatory complaints not presenting a keratinisation disorder;
- 4) for treating all dermal or epidermal proliferations, whether benign or malignant, whether or not of viral origin, such as common verrucas, plain verrucas or verruciform epidermodysplasia, oral or florid papillomatoses, and the proliferations that may be induced by ultraviolet radiation, particularly in the case of baso- and spinocellular epitheliomas;
- 5) for treating other dermatological disorders such as bullate dermatoses and collagenic diseases;
- 6) for treating certain ophthalmological disorders, particularly corneopathies;
- 7) for repairing or controlling ageing of the skin, whether photo-induced or chronological, or for reducing pigmentations and actinic keratoses, or any pathologies associated with chronological or actinic aging;
- 8) for preventing or curing stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;
- 9) for preventing or treating scarring disorders or for preventing or repairing stretch marks;
- 10) for controlling disorders of the sebaceous function, such as acne hyperseborrhoea or simple acne or seborrhea;
- 11) in the treatment of or prevention of cancerous or pre-cancerous conditions;
- 12) in the treatment of inflammatory complaints such as arthritis;
- 13) in the treatment of any complaint of viral origin affecting the skin or generally;
- 14) in the prevention or treatment of alopecia;
- 15) in the treatment of dermatological or general disorders with an immunological component;

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- 16) in the treatment of disorders of the cardiovascular system, such as arteriosclerosis."

Giacomoni's invention is primarily directed toward using their claimed compositions to reduce the skin irritant effect of topically applied cosmetic or pharmaceutical substances (see e.g. Giacomoni's abstract). The passage reproduced above at best represents unsubstantiated conjecture by Giacomoni. At worst, Giacomoni's teaching represents improper picking and choosing as Giacomoni presents a vast array of ailments to be treated without providing any direction or guidance for any of them. It has previously been held that when confronted with such a dizzying array of choices, the effect is that none of the choices are obvious without further direction (see e.g. *In re Rice*, 178 USPQ 478, 480 (CCPA 1973) - "...the board said, referring to the appellant's ingredients, 'It should be noted that an infinite number of combinations is possible.' Accepting that as an approximation to the truth, we fail to see the obviousness in devising appellant's.....[invention] as claimed.")

Furthermore, the claims as amended state that the compositions used in the claimed method of treatment of rosacea consist essentially of NO-synthase inhibitors and salts thereof. Even if it could be shown that the above passage from Giacomoni was enabling and provided adequate guidance towards the treatment of rosacea, it is only in the context of "...these treatments being particularly well adapted **when these compositions contain retinoids...**" Giacomoni does not teach or suggest that the broader scope of treatments would be effective in the absence of retinoids.

Preponderance of evidence standard for obviousness is not supported by Giacomoni
MPEP 2142 states:

"The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness [page 2100-123]...The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it.

With regard to the rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e. the reference teachings establish a *prima facie* case of obviousness) is more probable than not."

While the applicants concede that the evidence of record is less than 100% for non-obviousness, the applicants hold that the evidence in support of a holding of *prima facie* obviousness presented by the examiner does not meet the greater than 50% standard (i.e. preponderance of evidence) required to maintain a *prima facie* holding of obviousness especially when viewed in light of the teachings of Giacomoni for the broader methods of use and the requirement that retinoids be part of the compositions used in Giacomoni's method of use.

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- (2) Claims 1, 2, 4-8, 11-15 and 18-24 were rejected by the examiner as being obvious over Breton et al. (WO 97/15280)

A certified English language translation has been submitted with this response to perfect the claim for foreign priority of DE 197 11 565 (filing date 20 March 1997). Therefore, this rejection has been rendered moot as Breton et al. WO 97/15280 (publication date 1 May 1997) is no longer an eligible reference.

- (3) Claims 20-24 were rejected by the examiner as being obvious over Giacomoni (WO 96/26711) in view of Breton et al. (U.S. Patent 5,795,574).

For the reasons given above, this rejection has been rendered moot as Breton et al. WO 97/15280 (publication date 1 May 1997) is no longer an eligible reference.

Closing

Applicants also believe that this application is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

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By: 

Agata Glinska

19 Federal Republic
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The following information is taken from documents submitted by the applicant.

54 Preparations for the treatment of rosacea

57 The object of the invention is the use, in particular
the topical use, of a compound or a plurality of
compounds selected from the group of NO synthase
inhibitors and derivatives thereof for the prevention
and/or treatment of rosacea and cuperosis.

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Description

The object of the invention is topical cosmetic or dermatological preparations suitable for the treatment of rosacea. The manifestations of cuperosis are also included here as rosacea.

Rosacea is an inflammatory disease, preferentially of the face, accompanied by pronounced erythema, papules, and pustules of varying duration. Telangiectasia and elastosis are common, and the intrafollicular aggregation of neutrophils is also observed. The skin of rosacea patients is extraordinarily sensitive to chemical toxins and physical stressors, such as UV light. The pathogenesis is unclear.

Rosacea is not curable, but it can be treated with antibiotics, isotretinoin, fungicides such as metronidazole, or beta-blockers.

In contrast to many skin disorders which are accompanied by the massive influx of leucocytes, the infiltration of leucocytes in the vicinity of blood vessels and sebaceous glands is moderate.

The question has been raised in the literature as to whether the difficult to treat erythema of rosacea patients could be reduced by the use of NO synthase inhibitors (Qureshi, A.A. et al.; Arch. Dermatol. Vol. 132, Aug. 1996, 889-893). However, an answer has not been provided.

Only in the advanced state of rosacea are telangiectasia, papules, pustules, and tissue overgrowth such as rhinophyma observed, in addition to various forms of erythema. These manifestations are surgically treated.

On the whole, the success of pharmacological treatment of rosacea has not been satisfactory.

The object of the invention, therefore, is to provide a remedy, and in particular to provide active substances and preparations, by which rosacea, especially the incipient forms of this disease, may be safely treated without side effects.

These objects are achieved by the invention.

An object of the invention is the use, in particular the topical use, of a compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof for the prevention and/or treatment of rosacea and cuperosis.

A further object of the invention is the use of cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof for the prevention and/or treatment of rosacea and cuperosis.

A further object of the invention is cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof.

Examples of suitable NO synthase inhibitors include the following:

2-Iminobiotin,

L-N⁵-(1-Iminoethyl)-ornithine (L-NIO),

S-Methylisothiourea

S-Methylisothiourea sulfate (SMT),

S-Methyl-L-thiocitrulline,

L-N^G-(1-Iminoethyl)-lysine (L-NIL),

7-Nitroindazole (7-Ni),

S,S'-1,3-Phenylene-bis-(1,2-ethane-di-yl)-bis-isothiourea (PBITU)

L-Thiocitrulline (2-thioureido-L-norvaline),

and derivatives thereof.

Suitable derivatives are, for example, the monoalkylated or dialkylated inventive compounds of imino groups or amino groups.

In each case, the alkyl radicals of the monoalkyl groups or dialkyl groups may contain 1 to 10, preferably 1 to 6, in particular 1, 2, or 3 carbon atoms, and may be straight-chained or branched.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of carboxylic acid groups of the inventive compounds with alcohols are also preferred.

Preferred salts are water-soluble salts such as sodium, potassium, and ammonium salts. This applies to the acid addition salts as well. Suitable acid addition salts are obtained using inorganic and organic acids, for example. The hydrochlorides, phosphates, sulfates, acetates, caprylates, citrates, lactates, malates, or tartrates are preferred.

Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably monoalcohols. The alcohols may be straight-chained or branched, and may contain 1 to 12, preferably 1 to 6, carbon atoms. Methanol, ethanol, n-propanol, and isopropanol are preferred.

The esters are particularly preferred derivatives, and are also characterized by better penetration.

The compounds according to the invention are known, commercially available, or may be obtained by known methods. Their activity as NO synthase inhibitors is described in the literature.

Particularly preferred are NO synthase inhibitors according to the invention which contain an arginine group and derivatives thereof, in particular as described below.

An object of the invention, therefore, is in particular the use, in particular the topical use, of one compound or a plurality of compounds selected from the group comprising N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof for the prevention and/or treatment of rosacea and cuperosis.

A further object of the invention in particular is the use of cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group comprising N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof for the prevention and/or treatment of rosacea and cuperosis.

A further object of the invention is cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group comprising N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof.

In each case the alkyl radicals of the monoalkyl groups or dialkyl groups may contain 1 to 10, preferably 1 to 6, in particular 1, 2, or 3 carbon

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atoms, and be straight-chained or branched.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of carboxylic acid groups of arginine with alcohols are also particularly preferred.

Preferred salts are water-soluble salts such as sodium, potassium, and ammonium salts. This applies to the acid addition salts as well. Suitable acid addition salts are obtained using inorganic and organic acids, for example. The hydrochlorides, phosphates, sulfates, acetates, caprylates, citrates, lactates, malates, or tartrates are preferred.

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Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably monoalcohols. The alcohols may be straight-chained or branched, and may, for example, contain 1 to 12, preferably 1 to 6, carbon atoms. Methanol, ethanol, n-propanol, and isopropanol are preferred.

The esters are particularly preferred derivatives, and are also characterized by better penetration.

These compounds according to the invention are also known, commercially available, or may be obtained by known methods. Their activity as NO synthase inhibitors is described in the literature.

The following compounds are preferred:

NG-Monomethyl-L-arginine,
NG-Monoethyl-L-arginine,
NG-Nitro-L-arginine,
NG-Nitro-L-arginine-methyl ester,
NG-Nitro-L-arginine-ethyl ester,
NG-Monomethyl-L-arginine-methyl ester,
NG-Monoethyl-L-arginine-ethyl ester,
NG-Monomethyl-L-arginine-ethyl ester,
NG-Monoethyl-L-arginine-ethyl ester, and
NG, NG'-Dimethyl-L-arginine,
NG, NG'-Dimethyl-arginine,
NG, NG'-Dimethyl-L-arginine dihydrochloride, and
NG, NG'-Dimethyl-L-arginine dihydrochloride.

The following compounds are particularly preferred:

NG-monomethyl-L-arginine monoacetate (L-NMMA),
NG-monoethyl-L-arginine monoacetate (L-MEA),
NG-nitro-L-arginine (L-NNA), and
NG-nitro-L-arginine-methyl ester hydrochloride (L-NAME);
NG-nitro-L-arginine-methyl ester, or
L-NAME is very particularly preferred.

The inventive dermatological and cosmetic topical preparations may contain one NO synthase inhibitor or a plurality of NO synthase inhibitors, for example one, two, or three compounds, as active substance.

If preparations contain two or more of the active substances according to the invention, those preparations containing at least one NO synthase inhibitor with one arginine group are particularly preferred, in particular one of the aforementioned active substances containing an arginine group.

Particularly preferred are active substance combinations and preparations containing L-NAME and/or L-NMMA.

The active substances containing one arginine group may be contained in the combinations, for example in quantities of 10-90% by weight, in particular 30-70% by weight, in each case relative to the total weight of the active substances.

The compounds according to the invention and the dermatological and cosmetic topical preparations are thus very well suited for treatment and preventive treatment of couperosis and rosacea, in particular for stages I or II.

Surprisingly, the active substances and preparations according to the invention exhibit long-lasting, continuous activity during administration. Even after treatment is concluded, the skin remains symptom-free or significantly improved for a long time, possibly several weeks.

The cosmetic or dermatological topical preparations according to the invention may be based on per se conventional formulation bases, and may be used for treatment of the skin in the sense of dermatological treatment or for treatment in the sense of cosmetic use.

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The inventive, in particular topical, administration of NO synthase inhibitors surprisingly results in a reduction in cutaneous bleeding and, therefore, in decreased erythema. The resulting intensified infiltration of leucocytes and other immune cells leads to improved healing of the inflamed tissue.

The stated objects of the invention are thus achieved.

The inventive active substances and/or derivatives thereof are preferably contained in the topical cosmetic and dermatological preparations according to the invention in quantities of 0.001 to 20% by weight, particularly preferably 0.01 to 10% by weight, in particular 0.1 to 5% by weight, in each case relative to the total preparation.

Surprisingly, according to the invention the symptoms of rosacea, in particular erythema, are alleviated or prevented.

Particularly advantageous preparations are also obtained when the active substances according to the invention are combined with antioxidants.

The antioxidants according to the invention may advantageously be selected from the group of conventional cosmetic and dermatological

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antioxidants, in particular from the group comprising tocopherols and derivatives thereof, particularly γ -tocopherol or γ -tocopheryl esters, in particular γ -tocopheryl acetate, in addition to sesamol, gallic acid derivatives such as methyl, ethyl, propyl, amyl, butyl, and lauryl gallate, the coniferyl benzoate of benzoin resin, nordihydroguaiac resin acid, nordihydroguaiaretic acid, butylhydroxyanisole, butylhydroxytoluene, ascorbic acid, citric acid, phosphoric acid, lecithin, trihydroxybutyrophenone, carotenes, vitamin A and its derivatives, in particular retinyl palmitate, ascorbic acid, ascorbyl palmitate, dilauryl thiodipropionate, distearyl thiodipropionate, monoisopropyl citrate, thiodipropionic acid, EDTA and EDTA derivatives, cysteine, glutathione and its esters, uric acid, fipic acid, and its esters, carotene, heavy metal complexing agents such as delta-aminolevulinic acid and phytic acid, and Desferal® (Ciba-Geigy) and flavonoids, for example 4'-alpha-glucopyranosyl rutin.

The cosmetic or dermatological preparations according to the invention preferably contain 0.01 to 10% by weight, in particular 0.1 to 6% by weight, relative to the total weight of the preparations, of one or more substances from the group of antioxidants.

The antioxidants according to the invention are preferably selected from the group of flavonoids, or the tocopherols and derivatives thereof.

The preparations are administered in the manner typical for cosmetics or dermatological agents by applying sufficient quantities to the skin one or more times per day.

Skin care preparations and sun protection preparations are particularly preferred.

Dermatological and cosmetic preparations according to the invention may exist in various forms. Thus, for example, aqueous, alcoholic, or aqueous-alcoholic solutions, oil in water (O/W) emulsions, water in oil (W/O) emulsions, multiple emulsions such as water in oil in water (W/O/W) emulsions, gels, hydrodispersions, solid sticks, or aerosols may contain the aforementioned active substance combinations. Also preferred are low-water or water-free ointments and preparations.

The topical preparations according to the invention may contain conventional adjuvants such as emulsifiers and preservatives.

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Also preferred are cosmetic and dermatological preparations in the form of sun protection agents. These preparations also preferably contain at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment. Preparations containing one or more UVA filters are particularly preferred. UVA filters with strong absorption at 340 nm are particularly preferred.

Also advantageous are preparations applied to the skin following light exposure, such as après soleil products. For such preparations, it is within the discretion of one skilled in the art as to whether additional UV filtering substances should be used.

Cosmetic preparations according to the invention for protecting the skin from UV rays may exist in various forms as are typically used for this type of preparation. Thus, they may be, for example, an aqueous, alcoholic, or aqueous-alcoholic solution, an oil in water (O/W) or a water in oil (W/O) emulsion, or multiple emulsions such as water in oil in water (W/O/W) emulsions, gel, hydrodispersion, oil, solid stick, or aerosol.

The topical preparations according to the invention may contain dermatological and cosmetic adjuvants as are typically used in such preparations, for example preservatives, bactericides, fragrances, anti-foaming agents, dyes, pigments that impart color, thickeners, surface-active substances, emulsifiers, softeners, moisturizers or moisture retainers, fats, oils, waxes, or other typical components of a cosmetic formulation, such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents, or silicone derivatives.

If the cosmetic or dermatological preparation is a solution or lotion, the following may be used as solvents:

- Water or aqueous solutions;
- Oils such as triglycerides of capric or caprylic acid, preferably castor oil;
- Fats, waxes, and other natural and synthetic adipoids, preferably esters of fatty acids with alcohols having a low C number, for example isopropanol, propylene glycol, or glycerin, or esters of fatty alcohols with alkanolic acids having a low C number, or with fatty acids;
- Alcohols, diols, or polyols having a low C number and their ethers, preferably ethanol, isopropanol, propylene glycol, glycerin, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl, or monobutyl ether, diethylene glycol monomethyl or monoethyl ether, and analogous products.

Mixtures of the aforementioned solvents are used in particular. For alcoholic solvents, water may be an additional component.

Oils or emulsions according to the invention, for example in the form of sun protection cream, sun protection lotion, or sun protection milk, are advantageous, and contain for example the referenced fats, oils, waxes, and other adipoids in addition to water and an emulsifier as typically used for such a formulation.

Cosmetic and dermatological preparations for treatment and care of the skin may exist as gels, which, in addition to the active substances and solvents typically used therefor, also contain organic thickeners such as gum arabic, xanthan gum,

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sodium alginate, cellulose derivatives, preferably methylcellulose, hydromethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or inorganic thickeners such as aluminum silicates, for example bentonites, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. The thickener is contained in the gel in a quantity between 0.1 and 30% by weight, preferably between 0.5 and 1.5% by weight, for example.

Gels according to the invention typically contain alcohols having a low C number, for example ethanol, isopropanol, 1,2-propanediol, or glycerin, and water or an aforementioned oil in

the presence of a thickener, which, for oil-alcohol gels, is preferably silicon dioxide or an aluminum silicate, and which, for aqueous-alcohol or alcohol gels is preferably a polyacrylate.

Hydrodispersions are dispersions of a liquid, semisolid, or solid internal (discontinuous) lipid phase in an external aqueous (continuous) phase.

In contrast to O/W emulsions, which are characterized by a similar phase configuration, hydrodispersions are essentially free of emulsifiers. Hydrodispersions, and also, incidentally, emulsifiers, represent metastable systems and tend to convert to a state of two discrete phases merging into one another. The choice of a suitable emulsifier prevents phase separation in emulsions.

For hydrodispersions of a liquid lipid phase in an external aqueous phase, the stability of such a system can be ensured, for example, by forming in the aqueous phase a gel structure in which the lipid drops are stably suspended.

Solid sticks according to the invention may contain natural or synthetic waxes, fatty alcohols, or fatty acid esters, for example. Lip care sticks

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are preferred.

As propellants for cosmetic or dermatological preparations according to the invention which can be sprayed from aerosol containers, the commonly known low-volatility, liquid propellants such as hydrocarbons (propane, butane, isobutane) are suitable, which can be used singly or in mixtures with one another. The use of compressed air is also advantageous.

Of course, it is known to one skilled in the art that there are per se non-toxic propellant gases which would be fundamentally suitable for the present invention, but which should be avoided because of harmful effects on the environment or other circumstances, in particular fluorocarbons and chlorofluorocarbons (CFC).

Preferably, the preparations according to the invention may also contain substances which absorb UV radiation in the UVB range, whereby the total quantity of filter substances is, for example, 0.1 to 30% by weight, preferably 0.5 to 10% by weight, in particular 1 to 6% by weight, relative to the total weight of the preparation, to provide preparations which protect the skin from the entire range of ultraviolet radiation. They may also be used as sun protection agents.

The UVB filters may be oil-soluble or water-soluble. Examples of oil-soluble substances include the following:

- 3-Benzylidene camphor derivatives, preferably 3-(4-methylbenzylidene) camphor or 3-benzylidene camphor;
- 4-Aminobenzoic acid derivatives, preferably 4-(dimethylamino)-benzoic acid (2-ethylhexyl) ester, or 4-(dimethylamino)-benzoic acid amyl ester;
- Esters of cinnamic acid, preferably

4-Methoxycinnamic acid (2-ethylhexyl) ester or

4-methoxycinnamic acid isopentyl ester;

- Esters of salicylic acid, preferably Salicylic acid (2-ethylhexyl) ester, salicylic acid (4-isopropylbenzyl) ester, or salicylic acid homomenthyl ester;
- Derivatives of benzophenone, preferably 2-Hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methylbenzophenone, or 2,2'-dihydroxy-4-methoxybenzophenone;
- Esters of benzylidene malonic acid, preferably 4-methoxybenzylidene malonic acid-di(2-ethylhexyl) ester; and
- 2,4,6-Trianiino-(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5-triazine.

Examples of water-soluble substances include the following:

- Salts of 2-phenylbenzimidazole-5-sulfonic acid, such as the sodium, potassium, or triethanolammonium salt thereof, as well as the sulfonic acid itself;
- Sulfonic acid derivatives of benzophenone, preferably 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid and its salts;
- Sulfonic acid derivatives of 3-benzylidene camphor, for example 4-(2-oxo-3-benzylidene methyl) benzenesulfonic acid, 2-methyl-5-(2-oxo-3-benzylidene methyl) sulfonic acid, and the salts thereof.

A further object of the invention is the combination of inventive active substances with one or more UVA and/or UVB filters, or inventive cosmetic or dermatological preparations which also contain one or more UVA and/or UVB filters.

It may also be particularly advantageous to combine the active substances with UVA filters which are also typically contained in cosmetic and/or dermatological preparations. These substances are preferably derivatives of dibenzoylmethane, in particular 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl) propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl) propane-1,3-dione. These combinations, or preparations containing these combinations, are also an object of the invention. The quantities stated for the UVB combination may be used.

Advantageous preparations are also obtained when the active substances according to the invention are combined with UVA and UVB filters.

In addition, combinations of the active substances according to the invention with one or more antioxidants and one or more UVA filters and/or one or more UVB filters are particularly advantageous according to the invention.

The cosmetic or dermatological preparations may also contain inorganic pigments typically used in cosmetics for protecting the skin from UV rays. These include oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminum, cerium, and mixtures thereof, as well as variations in which the oxides are the active agents. Preferably preferred are pigments based on titanium dioxide.

A further object of the invention is the method for producing the topical preparations according to the invention, characterized by incorporation of the active substances into cosmetic or dermatological formulations in a known manner.

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Unless noted otherwise, all quantities, proportions, and percentages are based on the weight and total quantity, or total weight, of the preparations.

The following examples are intended to illustrate the present invention without limiting same.

The following compounds are used in the examples:

NG-Monomethyl-L-arginine monoacetate (L-NMMA),

NG-Monoethyl-L-arginine monoacetate (L-MEA),

NG-Nitro-L-arginine (L-NNA), and

NG-Nitro-L-arginine-methyl ester hydrochloride (L-NAME).

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Example 1

Sun gel (transparent)

	% by weight
L-NAME	1
Benzophenone-4	0.5
Phenylbenzimidazole sulfonic acid	1.3
Acrylamide/sodium acrylate copolymer	1.6
Ethanol	5.0
Glycerin	15.0
NaOH (15%)	as needed
Fragrance, preservative	as needed
Water, 100% deionized	to give 100.0

Example 2

Hydrodispersion

	% by weight
L-NMMA	5.0
Phenyltrimethicone	1.0
Carbomer (Carbopol 981)	1.0
Hydroxypropylmethylcellulose	0.2
Butylene glycol	3.0
Tromethamine	as needed
EDTA solution (14%)	0.5
Ethanol	5.0
Fragrance, preservative	as needed
Water, 100% deionized	to give 100.0

Example 3

O/W sun milk

	% by weight
L-MEA	2.5
Urea	5.0
Octylmethoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearyl alcohol + PEG-40 castor oil	+2.5
sodium cetearyl sulfate	
Glycerol lanolate	1.0
Laurylmethicone copolyol	0.5
Mineral oil (DAB 9)	5.0
Caprylic/capric triglycerides	5.0
Acrylamide/sodium acrylate copolymer	0.3
Cyclomethicone	2.0
TiO ₂	1.0
Glycerin	3.0
EDTA solution (14%)	0.5
Ethanol	5.0
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 4

W/O skin care lotion

	% by weight
L-NNA, HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7

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PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 5

O/W face care creme

	% by weight
L-NMMA	2.50
PEG-5 glyceryl stearate	2.00
Glyceryl stearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglycerides	3.00
Cetyl alcohol	3.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopheryl acetate	0.50
Glycerin	4.00
Fragrance, preservative	as needed
Water, deionized	to give 100.00

Example 6

W/O creme

	% by weight
L-NMMA	2.5
PEG-22 dodecyl glycol copolymer	3.0
Cetyl dimethicone copolyol	2.0
Cyclomethicone	4.0
Mineral oil (DAB 9)	4.0
Caprylic/capric triglycerides	4.0
Glycerin	4.0
Fragrance, preservative	as needed
Water, deionized	to give 100.00

Example 7

After sun lotion

	% by weight
I-NAME	5.00
Cetearyl alcohol + PEG-40 castor oil	+2.50
sodium cetearyl sulfate	
Glyceryl stearate SE	0.60
Mineral oil (DAB 9)	4.00
Caprylic/capric triglycerides	2.00
Shea butter	2.00
Avocado oil	2.00
Tocopheryl acetate	3.00

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Acrylamide/sodium acrylate copolymer	0.30
Glycerin	4.00
Hyaluronic acid	0.05
Bisabolol	0.05
Fragrance, preservative	as needed
Water, deionized	to give 100.00

Example 8

Shower milk

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	% by weight
L-MEA	5.0
Sodium laureth sulfate	11
Cocamidopropyl betaine	5
Cocamide DEA	1
PEG-8	1
Soybean oil	1
Citric acid	0.1
Sodium chloride	0.2
Fragrance	0.1
Water, demineralized	to give 100.0

Example 9

Skin care stick

	% by weight
1,2-Propylene glycol	11.0
Oleyl alcohol	14.0
Eosine dyes	3.0
Stearamide MEA (Kewamid S 280)	10.0
Beeswax	10.0
Glycerin monostearate	10.0
Cetyl alcohol	10.0
Ceresine wax	8.0
Stearyl heptanoate (CI, solid)	6.0
Lanolin, anhydrous	6.0
Pigments and toners	6.0
Fragrance oil	1.0
L-NAME	5.0

Example 10

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and)	65
octyldodecanol (and) carnauba (and)	
candelilla wax (and) microcrystalline (and)	
cetyl alcohol (and) beeswax (and) mineral	
oil Cutina LM (Henkel)	
Caprylic/capric triglycerides (Myristol 318)	20
Pigment colors	3.0
Titanium dioxide	7.0
L-NMMA	4.0
L-NIO	1.0

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Example 11

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and)	78.0
octyldodecanol (and) carnauba (and)	
candelilla wax (and) microcrystalline	
(and) cetyl alcohol (and) beeswax (and)	
mineral oil Cutina LM (Henkel)	
Octyldodecanol (Eutanol G)	15.0
Coloring pigments	2.0
L-NMMA	4.0
L-NIL	1.0

Example 12

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W/O skin care lotion

	% by weight
2-Iminobiotin	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 13

W/O skin care lotion

	% by weight
L-NIO-HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 14

W/O skin care lotion

	% by weight
S-Methylisothiurea sulfate	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7

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Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 15

W/O skin care lotion

	% by weight
S-Methyl-L-thiocitrulline	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 16

W/O skin care lotion

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	% by weight
L-NIL-2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 17

W/O skin care lotion

	% by weight
7-Nitroindazole	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 18

W/O skin care lotion

% by weight

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PBITU-2HBr	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Example 19

W/O skin care lotion

% by weight

L-Thiocitrulline-2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerin sorbitan oleostearate	1.7
PEG-7 hydrated castor oil	6.3
Mineral oil (DAB 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerin	4.0
MgSO ₄	0.7
Fragrance, preservative	as needed
Water, deionized	to give 100.0

Claims

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1. Use of one compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.
2. Use of cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.
3. Cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors and derivatives thereof.
4. Use according to Claim 2, characterized in that the preparations contain at least one antioxidant.
5. Use according to Claim 2, characterized in that the preparations contain at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.
6. Use according to Claim 2, characterized in that the preparations contain at least one antioxidant and at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.
7. Use of one compound or a plurality of compounds according to Claim 1, selected from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G'-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.

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8. Use of cosmetic or dermatological topical preparations according to Claim 2, containing one compound or a plurality of compounds selected from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G'-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.
9. Cosmetic or dermatological topical preparations according to Claim 3, containing one compound or a plurality of compounds selected from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, N^G'-dialkyl-L-arginine, and N^G-nitro-L-arginine and derivatives thereof.
10. Use or preparation according to Claims 7 through 9, characterized in that N^G-nitro-L-arginine-methyl ester or N^G-nitro-L-arginine-methyl ester hydrochloride is used.
11. Use according to Claim 8, characterized in that the preparations contain at least one antioxidant.
12. Use according to Claim 8, characterized in that the preparations contain at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.
13. Use according to Claim 8, characterized in that the preparations contain at least one antioxidant and at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.
14. Use of one compound or a plurality of compounds selected from the group of NO synthase inhibitors containing an arginine group and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.
15. Use of cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors containing an arginine group and derivatives thereof for the prevention and/or treatment of rosacea and couperosis.
16. Cosmetic or dermatological topical preparations containing one compound or a plurality of compounds selected from the group of NO synthase inhibitors containing an arginine group and derivatives thereof.

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